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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,492	08/18/2000	Gary Van Nest	377882000800	7136

25226 7590 06/02/2003

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,492	VAN NEST ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2003 and 12 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,11,13-23,25-33 and 37-53* is/are pending in the application.

4a) Of the above claim(s) *43-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,11,13-23,25-33,37-42 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

In paper no. 22, applicant cancelled claim 12, amended claims 1, 11, 37, 40 and added new claim 53. Claims 1, 4-6, 11, 13-23, 25-33 and 37-53 are pending, claims 43-52 are withdrawn due to a non-elected invention and claims 1, 4-6, 11, 13-23, 25-33, 37-42 and 53 are under consideration.

Request for Continued Examination

The request filed on 2/13/3 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/642492 is acceptable and a RCE has been established. An action on the RCE follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-6, 11, 13-23, 25-33, 37-42 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 37, 40 and 53 comprise a complex comprising an immunostimulatory sequence (ISS) and a first antigen. The claims state that the ISS sequence and the first antigen are "proximately associated". Since the claims state that the ISS and first antigen are in a complex, the molecules being "proximately associated" appears to be redundant and confuses the relationship between the two molecules. On page 6, lines 19-26 and page 13, line 30 to page 14, line 5, the specification defines proximal association by conjugation, encapsulation, adsorption to a surface or linkage to a platform molecule. Merriam-Webster's Collegiate Dictionary, 10th

edition. 1993; Springfield, MA: Merriam-Webster, Incorporated, defines "complex" as a chemical association of two or more species joined by weak electrostatic bonds, rather than covalent bonds, see the citation on page 235 provided. Therefore, complex of the claims would encompass all of the examples presented in the specification for proximate association. It is suggested that applicant amend the claims delete all "proximately associated" language from the claims. After the amendment, the claims would recite, "(i) a complex comprising an immunomodulatory polynucleotide and a first antigen" in the first portion of the claims. This suggested language clearly conveys that the ISS and first antigen are a complex and that that second antigen would not be a part of the complex because it is separately designated as component (ii). This rejection also affects claims 4-6, 11, 13-23, 25-33, 38, 39, 41 and 42.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 11, 13-23, 25-33 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulating a Th-1 immune response by increasing an IgG2a response and decreasing an IgG1 response against a second antigen by co-administering the second antigen with an ISS-antigen complex, does not reasonably provide enablement for modulating a Th-1 response against a second antigen that is administered after the administration of an ISS-antigen complex or modulating a Th-1 response to a second antigen that is co-administered with the ISS-antigen complex at a different site of administration from the ISS-antigen complex. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The claims are drawn to a method of modulating an immune response to a second antigen by co-administering a complex comprising (i) an immunostimulatory sequence (ISS) and a first antigen and (ii) a second antigen. The claims encompass non-enabling embodiments of modulating an immune response against a second antigen that is administered after the administration of the ISS-antigen complex and modulating an immune response against a second antigen that is co-administered in a different location from the ISS-antigen complex.

The nature of the invention

The nature of the invention is drawn to modulating an immune response, specifically a Th-1 response, against a second antigen that is administered with a complex comprising an ISS-antigen conjugate.

The state of the prior art

The prior art demonstrates that co-administration of ISS molecules and an un-complexed antigen generate a Th-1 immune response. Horner et al. (Cellular immunology. 1998; 190: 77-82) teach co-administering β-gal and an ISS molecule as a mixture at the same time and site of delivery to generate a Th-1 response, see "Immunization protocols" on page 78 and "Immunization with β-gal and ISS-ODN..." bridging pages 79-80. Chu et al. (Journal of Experimental Medicine. 1997; 186 (10): 1623-1631) teach immunostimulatory CpG dinucleotides induce a Th-1 response upon co-administration with hen egg lysozyme (HEL), see "Immunizations" on page 1624 and the results section bridging pages 1625-1628. The prior art does not teach generating a Th-1 response by administering an antigen at a different site of

delivery from the ISS molecule or inducing a Th-1 response against an antigen that is administered subsequently to the ISS molecule.

The level of one of ordinary skill

It is within the level of skill for one in the art to administer an antigen at a site different from the site of administration of the ISS nucleotide sequence and to administer the antigen and ISS components at different time periods. However, it is not within the skill of one in the art to generate a Th-1 response against an antigen that is administered at a different site and/or time from the ISS molecule because the working example on pages 52-56 clearly indicate that this type of induction is not enabled by these routes of administration.

The level of predictability in the art

Since the art does not disclose a method of modulating a Th-1 immune response against an antigen that is administered at a different site and/or time from administration of an ISS sequence, the skilled artisan would not predict, in the absence of proof to the contrary, that a Th-1 response could be generated by such administrations. The claims encompass modulating an immune response against an antigen that is administered at a different location and/or time period from the immunostimulatory sequence. The assertion of a broad application as set forth in the instant method claims necessarily requires evidence to support applicant's asserted methods.

The amount of direction provided by the inventor

Although the specification teaches administering a second antigen at a different site and time from the administration of an ISS molecule in example 1 on pages 52-56, the specification does not teach success for modulating an immune response to a second antigen that is administered by these methods. There is no guidance provided in the disclosure that would enable the skilled artisan to modulate an immune response against an antigen that is not co-administered with an ISS molecule.

The existence of working examples

The working example on pages 52-54 admittedly indicates that an ISS complex delivered before a β-gal antigen at the same site of administration does not induce an immune response against β-gal, see page 53, lines 5-7. The working example bridging pages 54-56 clearly indicates that co-administration of an ISS complex and β-gal at the same time, but at different locations, does not modulate an immune response against β-gal. This is also admitted on page 56, lines 3-11.

The quantity of experimentation needed to make or use the invention

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). There is not sufficient evidence in the disclosure to support applicant's claims encompassing modulating an immune response against an antigen that

is administered at a different location or time from delivery of an ISS molecule. Although the prior art does not teach administering an antigen at a different site or time from an ISS molecule, the working examples clearly indicate that the instant claims encompass subject matter that is not commensurate in scope with the enabling method of administration. The specification does not provide any guidance that would enable the skilled artisan to produce results different from those observed in the working examples. Therefore, it is determined that an undue quantity of experimentation would be required of the skilled artisan to use the invention commensurate in scope with the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 6, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (WO 98/55495, "Schwartz") for reasons of record.

Claims 1, 4, 6, 11, 13, 14, 17, 20-23, 32, 33 and 37 are drawn to a composition and a method of modulating a Th1 immune response to a second antigen by administering a complex comprising an immunostimulatory molecule (ISS) and a first antigen to modulate an immune response against a second antigen that is not proximately associated with the complex. The first antigen can be a variety of antigens, such as an allergen or a virus polypeptide, with a carrier

molecule. The ISS comprises various short sequence residues in claims 25-31. Claims 40-42 are drawn to a composition comprising an immunostimulatory polynucleotide (ISS) composition proximately associated with a first antigen that is an allergen, Amb a 1, and a second antigen.

Schwarz teaches an immunomodulatory composition comprising an ISS conjugated to AgE, also known as amb a1, page 30, lines 19 and 20 and page 31, lines 10-13, claims 25, 27 and Figure 7. Schwarz also teaches antigenic peptides derived from viruses are also administered in conjunction with an ISS sequence, see page 13, line 26 to page 14, line 3. Schwarz teaches administering the ISS conjugates in the same location in the patient, see page 24, line 23 to page 26, line 33. Schwartz also teaches the instant ISS sequences, including SEQ ID NO: 1, see the sequence alignment previously provided and/or SEQ ID NO: 2 of Schwarz as well as claims 2-5. Although Schwartz does not explicitly teach administering a second antigen with the composition, Schwartz suggests that the immunomodulatory compositions comprise at least one antigen, see page 5, lines 1-2 and page 12, lines 9-15. Schwartz also teaches co-administration of an admixture to modulate an immune response. Schwartz defines co-administration by administering two different substances sufficiently close in time to modulate an immune response. This teaching encompasses the co-administration of an ISS-antigen conjugate co-administered with a second antigen. Further, claims 25-27 of Schwartz are drawn to an immunostimulatory composition comprising an ISS oligonucleotide conjugated to an antigen. Claims 28 and 30 of Schwartz are drawn to immunomodulatory compositions comprising an ISS and an antigen or peptide. These claims encompass compositions comprising ISS and separate antigens. Therefore, Schwartz teaches immunomodulating an immune response with compositions comprising ISS-antigen complexes or ISS molecules and antigens that are not

contained within a complex. Therefore, administering a second antigen with a complex comprising an ISS-antigen complex would have been obvious from the teachings of Schwartz.

Applicant argues that Schwartz does not teach or suggest co-administering (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen and (ii) a second antigen. Applicant concludes that Schwartz does not provide a reasonable expectation for producing the claimed invention.

Applicant's arguments as well as a review of the reference have been considered, but are found unpersuasive. Schwartz teaches that ISS oligonucleotides are art-recognized as being Th1 stimulatory molecules when administered with an antigen, see page 3, lines 32-35 and claims 47 and 48. This Th1 stimulation is analogous to an adjuvanting effect with an ISS molecule. As discussed above, Schwartz explicitly induces a Th1 response by co-administering an antigen conjugated to an ISS oligonucleotide. Schwartz also claims compositions comprising ISS and separate antigens and teaches that the immunomodulatory compositions comprise at least one antigen, see page 5, lines 1-2 and page 12, lines 9-15. Absent unexpected results, one of ordinary skill in the art would have a more than reasonable expectation of inducing a Th1 response to any antigen that is complexed with an ISS molecule and any antigen that is co-administered with an ISS molecule. Therefore, although Schwarz does not explicitly teach inducing a Th1 response to an antigen that is administered with an ISS-antigen conjugate, one of ordinary skill in the art would expect induction of a Th1 against any of the complexed or non-complexed antigens. Therefore, co-administering a second antigen with an ISS-antigen complex and would be a prima facie obvious variation to the teachings of Schwartz.

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to administer a second antigen in order to elicit a specific immune response against another portion of a pathogen or another strain of virus. Schwartz also suggests administering more than one antigen, see see page 5, lines 1-2 and page 12, lines 9-15. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Schwartz teaches that antigens administered with an ISS molecule elicit a Th1 immune response. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent evidence to the contrary.

Applicant also points out that co-administering in the instant application encompasses administering the complex and the second antigen at different times. However, this embodiment is not commensurate in scope with the claims under the instant rejection.

Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33, 37 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson et al. (WO 98/16247, "Carson").

See the summary of the claims above.

Carson teaches an immunomodulatory composition comprising an ISS conjugated to AgE, also known as amb a1, see page 19, line 22, and Figures 3-5. Carson also teaches ISS partners include antigens from viruses, see page 18, lines 10-12. These ISS and antigen compositions also comprise carriers for various routes of administration, see page 26, line 24 to page 29, line 5. The sequences of the instant IS molecules are also taught by Carson, see page 4, lines 18-23, claims 3, 8-10 for example and the sequence alignment of SEQ ID NO: 1 with WO 98/16247. Geneseq database. Accession no: V32079. April 23, 1998, provided in Office action

mailed 7/30/02. Carson also teaches administering the complex at the same location in a patient, see page 26, line 24 to page 29, line 6. Although Carson does not explicitly teach administering a second antigen with the composition, Carson teaches that ISS molecules induce a Th-1 response to an antigen, see page 11, lines 21-28. Carson teaches administering an ISS-antigen complex and a mixture comprising ISS and an antigen to induce a Th-1 response to the antigen, see page 35, lines 10-17 and figure 1.

As applicant notes in the response, the advisory action stated that Carson did not observe a potentiated immune response with the ISS and antigen mixture. However, upon reconsideration of the reference data, it is determined that although the immunopotentiation observed with the ISS and antigen mixture is not as robust as the potentiation observed with the ISS-antigen conjugate, there is an increase in the level of IgG2a produced compared to β-gal administered alone or β-gal mixed with alum, see Figure 1. Therefore, the data of Carson indicate that an increase in IgG2a, which is indicative of a Th-1 response, is observed for ISS-antigen complexes as well as with a mixture of ISS and antigen. Therefore, administering an ISS-conjugate and a second, un-complexed antigen would have been prima facie obvious from the teachings of Carson. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a Th-1 response against a second antigen that is administered with an ISS-antigen complex because Carson teaches that ISS induces a Th-1 response against antigens that are administered with the ISS molecule, see Figure 1 and claims 54 and 66.

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to administer a second antigen in order to elicit a specific immune response

against another portion of a pathogen or another strain of virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Carson teaches that antigens administered with an ISS conjugate elicit a Th1 immune response. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent evidence to the contrary.

Applicant argues that Carson does not support a prima facie obvious case for inducing an immune response against a second antigen upon co-administration of a complex comprising an ISS-antigen and a second antigen.

Applicant's arguments have been fully considered, but are found unpersuasive. As discussed above, Carson teaches inducing a Th-1 response with an ISS-antigen complex and a mixture comprising ISS and an antigen. Therefore, it is determined that administering an ISS-antigen conjugate and a second antigen with the ISS-antigen conjugate would have been prima facie obvious from the teachings of Carson. Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for inducing an immune response against an antigen that is not conjugated with an ISS molecule because Carson teaches inducing IgG2a against an antigen present in a mixture with ISS. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al. as applied to claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Rose (J. Ther. Biol. 1998; 195: 111-128).

Claim 5 is drawn to an immunomodulatory polynucleotide and a first antigen proximately associated by a platform molecule.

See the teachings of Schwartz et al. or Carson et al. above. Neither reference teaches the use of a platform molecule.

However, Rose teaches using a platform molecule to treat cancer where the platform is an insoluble material that has the ability to bind various agents, see the last paragraph on page 111 through the of the introduction on page 112 and figure 1 on page 114. Since the teachings of Rose demonstrate that various components may be proximately associated by a platform molecule, the limitation of a platform molecule in claim 5 would have been an obvious modification to the other mechanisms of proximity taught by Schwartz et al. or Carson et al. and used without an unexpected result.

Applicant argues that Rose does not supply the missing element from Schwartz or Carson of potentiating an immune response against a second antigen that is co-administered with an ISS-antigen complex.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been obvious from the teachings of Schwartz or Carson because each reference individually teach inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, Rose is not needed to teach a limitation that is taught by the primary references.

Claim 15 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al. as applied to claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Lee et al. (Ann Med. 1998; 30: 460-468).

The claims are drawn to the viral polypeptide, where the polypeptide is an influenza nucleocapsid protein.

See the teachings of Schwartz et al. or Carson et al. above. Neither of the references teach influenza nucleocapsid protein.

However, Lee et al. teach that this protein is the least effected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection, see "infectious diseases" on page 465. One of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art would have had a reasonable expectation in producing the claimed invention because Schwartz or Carson teach compositions and methods comprising ISS and proteins that modulate the immune response and Lee et al. also teach subsequent Th1 responses upon administration of ISS with DNA encoded antigens, see "mechanism of action..." on pages 463-464. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant argues that none of the references alone or in combination teach potentiating an immune response against a second antigen that is co-administered with an ISS-antigen complex.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been obvious from the teachings of Schwartz or Carson. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, Lee is only required to teach a limitation that is not taught by the primary references.

Claims 16 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al., as applied to claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Durali et al. (J of Virol. 1998; 72(5): 3547-3553).

The claims are drawn to viral polypeptide, where the polypeptide is HIV gag.

See the teachings of Schwartz et al. or Carson et al. above. Neither of the references teach an influenza nucleocapsid protein or HIV gag in their compositions.

However, Durali et al. teach that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV, see the abstract. Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art would be motivated to incorporate this protein into a composition to induce an immune response against the antigen. Furthermore, the skilled artisan would have a reasonable expectation in producing the claimed invention because both Schwartz et al. and Carson et al. teach that the protein portion of the composition and method could be a wide variety of proteins from viruses, see previously cited excerpts.

Applicant argues that none of the references alone or in combination teach potentiating an immune response against a second antigen that is co-administered with an ISS-antigen complex.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been obvious from the teachings of Schwartz or Carson. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, Durali et al. is only required to teach a limitation that is not taught by the primary references.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al., as applied to claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Anderson (US Patent 4,673,574).

The claims are drawn to using diphtheria toxin mutant CRM 197 or diphtheria toxoid as a carrier molecule.

See the teachings of Schwartz or Carson above. Neither of the references teach using either diphtheria molecule.

Anderson teaches that diphtheria toxoid or diphtheria toxin mutant CRM 197 can be use as carriers in a vaccine preparations, see column 4, lines 35-68 and example 8 in column 14, line 9 through column 16, line 44.

One of ordinary skill in the art at the time the invention was made would have been motivated to use the diphtheria components taught by Anderson in the method and composition taught by taught by Schwartz et al. or Carson et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children, see column 5, lines 10-19 and column 14, table 7. One of ordinary skill in the art at the time the

invention was made would have had a reasonable expectation in producing the claimed invention because Schwartz et al. or Carson et al. teach that the ISS/antigen composition can be combined with any known vaccine component and the diphtheria toxins taught by Anderson are well known.

Applicant argues that none of the references alone or in combination teach potentiating an immune response against a second antigen that is co-administered with an ISS-antigen complex.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been prima facie obvious from the teachings of Schwartz or Carson. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, is Anderson is only required to teach a limitation that is not taught by the primary references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
May 30, 2003